The Risk of Developing Second Cancers among Survivors of Childhood Soft Tissue Sarcoma

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BACKGROUND. Previous studies have shown that children who are treated for soft tissue sarcoma (STS) are at increased risk for developing second cancers. However, the risk for specific cancer sites and variations in risk by treatment and STS histology remain unclear.

METHODS. The study evaluated 1499 children (age < 18 years) who survived for ≥ 1 year after they were diagnosed with STS and who were reported to the Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries from 1973 to 2000.

RESULTS. Twenty-seven children developed 28 subsequent primary malignancies, compared with 4.5 expected malignances based on general population rates (observed-to-expected [O/E] ratio = 6.3 (95% confidence interval [95% CI], 4.2–9.1). The risk of developing a subsequent malignancy was increased among children with rhabdomyosarcoma (observed = 11 malignancies; O/E ratio = 7.7), fibromatous neoplasms (observed = 9 malignancies; O/E ratio = 5.8), and other specified STS (observed = 7 malignancies; O/E ratio = 6.5). Initial therapy with radiation and chemotherapeutic agents was associated with a significantly higher risk of second malignancies compared with surgery alone (O/E ratio = 15.2 vs. 1.4; $P < 0.0001$). Elevated risks were observed for acute myeloid leukemia, cutaneous melanoma, female breast cancer, and sarcomas of the bone and soft tissue, with generally higher risks among patients who initially received combined modality therapy. Excess cancers of the oral cavity were prominent among long-term survivors. For several children, the pattern of multiple malignancies was consistent with a genetic syndrome, particularly neurofibromatosis type 1 and Li–Fraumeni syndrome.

CONCLUSIONS. The risk of second malignancies was increased for all histologic types of childhood STS and was particularly high among patients who received combined modality therapy. ***Cancer* 2005;103:2391–6.**
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KEYWORDS: second cancers, soft tissue sarcoma, rhabdomyosarcoma, fibrosarcoma, childhood cancer.

The survival of children with soft tissue sarcoma (STS) has improved substantially over the last 25 years.[1] As the number of long-term survivors has increased, concerns have heightened over the potential of late sequelae, especially the development of second malignancies.[2–8] These concerns are underscored by the association of childhood STS with genetic syndromes that predispose to multiple cancers, including neurofibromatosis type 1 (NF1) and Li–Fraumeni syndrome (LFS).[9] Estimates of the risk of subsequent malignancies after childhood STS have varied widely, ranging from 3 times to 13 times the number expected based on general population incidence rates.[4–6] Furthermore, the use of intensive chemoradiotherapy regimens for rhabdomyosarcoma, which is a major histologic type of

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pediatric STS, has been accompanied by clinical trial reports of treatment-related second cancers.[2,3] However, quantification of the risk of second cancer is limited by the heterogeneity in STS histologic types and the small size of many previous studies. For this report, we evaluated nearly 1500 children who were diagnosed with STS in population-based registries across the United States and estimated the relative and absolute risks of subsequent cancers by second cancer site, initial therapy, histologic type of STS, age at STS diagnosis, and gender.

MATERIALS AND METHODS

We identified 1499 children (age $<$ 18 years) who survived $\geq$ 1 year after an STS diagnosis from 1973 to 2000 and who were reported to 1 of 9 population-based registries from the Surveillance, Epidemiology, and End Results (SEER-9) Program of the National Cancer Institute. SEER records data on patient demographics, tumor site, morphology, grade, histologic confirmation, reporting source, date of diagnosis, cancer stage at diagnosis, first course of treatment, and follow-up for vital status, including cause of death. Subsequent primary cancers as well as the initial malignancy are reportable to SEER. The 9 registries included in this study are the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii ($\geq$ 1973); the metropolitan areas of Detroit and San Francisco-Oakland ($\geq$ 1973); the Seattle-Puget Sound area ($\geq$ 1974); and Atlanta ($\geq$ 1975).[10] Altogether, these 9 registries represent approximately 10% of the population in the United States. SEER-9 is comparable to the general United States population in terms of poverty level and educational measures, but the registries tend to be more urban with a higher proportion of foreign-born individuals.[11]

The cohort in this study included 800 males and 699 females. The histologic subtypes of STS were divided into three categories: rhabdomyosarcoma, fibromatous neoplasms, and other specified STS, as defined by the International Classification of Childhood Cancers.[12] The main types of rhabdomyosarcomas are embryonal and alveolar. Some of the common sarcomas that belong to the fibromatous category include fibrosarcoma, neurofibrosarcoma, and malignant neurilemmoma. Liposarcoma, leiomyosarcoma, and angiomyosarcoma are among the tumors categorized as "other specified STS." Overall, the median age at diagnosis was 10.3 years—6.3 years for rhabdomyosarcoma (n = 652 patients), 12.7 years for fibromatous neoplasms (n = 402 patients), and 13.1 years for other specified STS (n = 310 patients). Treatment information from SEER was limited to broad categories of first-course therapy (surgery, radiotherapy, chemotherapy, hormones, other, and unknown).

The observed numbers of subsequent primary cancers were compared with the expected numbers based on gender-specific, race-specific, age-specific, and calendar year-specific SEER incidence rates. Person-years at risk (PYR) were calculated from 12 months after initial STS diagnosis until the end of the study (December 31, 2000), the date of last follow-up, or the patient's death, whichever occurred first. The follow-up rate for this study was 90% through 1999 and 86% through 2000. In total, 13,455 PYR were accumulated for a median follow-up of 7.1 years (8.1 years from STS diagnosis). The study included 650 10 or more-year survivors. For statistical analyses, it was assumed that the observed numbers of subsequent malignancies followed a Poisson distribution. Absolute excess risk (AER) was defined as the observed minus expected number of second cancers per 10,000 PYR. The cumulative incidence of developing a subsequent malignancy at 20 years after STS diagnosis was calculated using second cancer as the event of interest and death due to all other causes, including first STS, as the competing risk.[13] Two-sided 95% confidence intervals (95% CIs) were calculated throughout.

RESULTS

Twenty-seven children developed 28 second primary cancers, compared with 4.5 expected malignancies (observed-to-expected [O/E] ratio = 6.3, 95% CI, 4.2–9.1) (Table 1). The AER was 17.5 additional cancers per 10,000 PYR. The cumulative incidence of second cancers was 2.9% (95%CI, 1.8–4.4%) at 20 years, with a 28.4% competing risk of death (95% CI, 25.6–31.1%) at 20 years. Significantly increased risks were found for second solid tumors combined, acute myeloid leukemia (AML), cutaneous melanoma, and cancers of the oral cavity and pharynx, female breast, bone, and soft tissue. The multiple cancer patterns for three children were suggestive of known genetic syndromes. One child developed a pattern of multiple cancers consistent with LFS: fibrosarcoma, osteosarcoma, and breast cancer at ages 8 years, 13 years, and 19 years, respectively. A second child with rhabdomyosarcoma followed by neurofibrosarcoma died of neurofibromatosis. The history of a third child with an initial diagnosis of neurilemmoma of the lower limb/hip followed by neurilemmoma of the thorax also was suggestive of neurofibromatosis.

The relative risk of developing a second cancer was highest during the first 5 years of follow-up, at almost 12 times the expected number, but decreased to 5-fold throughout the remaining follow-up intervals

TABLE 1
The Risk of Second Cancers among 1499 1-Year Survivors of Childhood Soft Tissue Sarcoma, Ages < 18 Years, by Second Cancer Site and Time since Initial Diagnosis

	Time since STS diagnosis									
	1–4 yrs		5–9 yrs		≥10 yrs		Total ≥ 1 yr			Absolute excess risk[a]
Second malignancy	Observed	O/E	Observed	O/E	Observed	O/E	Observed	O/E	95% CI	
All sites excluding nonmelanoma skin	9	11.7[b]	5	5.5[b]	14	5.0[b]	28	6.3[b]	4.2–9.1	17.5
All solid tumors	5	10.7[b]	4	6.5[b]	13	5.9[b]	22[c]	6.7[b]	4.2–10.1	13.9
Oral cavity and pharynx	0	—	0	—	3	52.6[b]	3[c]	33.9[b]	6.8–99.1	2.2
Colon excluding rectum	1	243.2[b]	0	—	0	—	1	13.9	0.2–77.6	0.7
Lung and bronchus	0	—	1	172.5[b]	0	—	1	17.2	0.2–95.7	0.7
Bones and joints	2	43.3[b]	2	48.3[b]	2	45.5[b]	6[d]	45.6[b]	16.7–99.3	4.4
Soft tissue including heart	0	—	1	27.5	1	16.1	2	14.4[b]	1.6–51.8	1.4
Melanoma of the skin	1	26.1	0	—	2	6.1	3	6.7[b]	1.4–19.6	1.9
Female breast	0	—	0	—	4	12.4[b]	4[e]	11.6[b]	3.1–29.8	5.9
Female genital system	1	29.2	0	—	1	3.5	2[f]	5.2	0.6–18.6	2.6
AML	4	141.5[b]	0	—	0	—	4[g]	39.2[b]	10.6–100.4	2.9
All other sites[h]	0	—	1	3.7	1	1.9	2	1.9	0.2–6.7	0.7

STS: soft tissue sarcoma; O/E: observed-to-expected ratio; 95% CI: 95% confidence interval; AML: acute myeloid leukemia.

[a] Absolute excess risk = [(observed-expected)/person-years at risk] × 10,000.

[b] Statistically significant ($P < 0.05$).

[c] Oral cavity and pharyngeal cancers included squamous cell cancers of the tonsils (1), tongue (1), and mouth (1).

[d] Histologic types of bone cancer included four osteosarcomas and two chondrosarcomas.

[e] The female breast category included one patient who developed a third primary breast cancer after a second primary osteosarcoma.

[f] Cancers of the female genital system included one ovarian cancer and one cancer of the uterine corpus.

[g] All 4 patients with AML were diagnosed 13–29 months after they were diagnosed with STS.

[h] All other sites included miscellaneous cancers (two observed cancers with an unknown primary site) and all lymphatic and hematopoietic cancers, excluding AML (no observed cancers).

(Table 1). The 4 patients with AML developed their cancer early, 13–29 months after STS diagnosis, and all of these children were treated initially for STS after 1985. In contrast, second solid malignancies of the bone, soft tissue, female breast, and oral cavity occurred later in the follow-up period, at median intervals of 99 months, 130 months, 148 months, and 192 months, respectively, after the initial STS diagnosis.

The relative risk of developing a new malignancy was substantially higher for children with STS who were treated in more recent calendar years (< 1985 vs. ≥ 1985: O/E ratio = 4.4 vs. 12.5, $P < 0.004$; data not shown). Children who were diagnosed with STS at ages < 10 years (observed = 11 malignancies; O/E ratio = 9.1) had higher relative risks of developing a subsequent cancer compared with patients who were diagnosed at older ages (observed = 17 malignancies, O/E ratio = 5.2), but the AERs were similar—an additional 15.4 cancers versus 19.3 cancers per 10,000 PYR. Slightly higher O/E ratios were found for females (observed = 16 malignancies; O/E ratio = 7.1) than males (observed = 12 malignancies; O/E ratio = 5.4). However, if gender-specific cancers of the breast and genital tract were excluded, then the risk of second cancers for females (O/E ratio = 6.6; 95% CI, 3.2–12.2) was nearly identical to that of males (O/E ratio = 6.6; 95% CI, 3.4–11.4).

Risk by Initial Treatment

Combined radiotherapy and chemotherapy was associated with a significantly higher risk of second cancer compared with surgery alone (O/E ratio = 15.2 vs. 1.4; $P < 0.0001$) (Table 2). Although the numbers were small for individual cancer sites, initial combined modality therapy was associated with significantly high risks of second sarcomas of the bone and soft tissue, female breast cancer, cutaneous melanoma, and AML. Initial therapy with radiation alone was associated with a nearly eight-fold risk of new malignancies, with two of the three cancers developing in the bone or soft tissue. Two of four second breast cancers, six of eight sarcomas of the bone and soft tissue, and one of three cancers of the oral cavity developed in or near the radiation field. In contrast, none of the three subsequent melanomas appeared to be located near the radiation field.

TABLE 2
The Risk of Second Cancers among 1-Year Survivors of Childhood Soft Tissue Sarcoma by Initial Treatment

Second cancer	No. of patients with STS	Median PYR	Total survivors ≥ 1 yr		
			Observed	O/E	95% CI
All second malignancies					
Surgery only	480	10.6	3	1.4	0.3–4.2
Radiotherapy only[a]	102	7.9	3	7.6[b]	1.5–22.1
Chemotherapy only[a]	318	4.7	2	3.5	0.4–12.8
Radiation and chemotherapy[a]	555	4.9	18	15.2[b]	9.0–24.0
Other and unknown[a]	44	13.4	2	8.6	1.0–30.9
Bones and soft tissue[c]					
Radiotherapy only	102	7.9	2	97.8[b]	11.0–353.1
Chemotherapy only	318	4.7	1	22.1	0.3–122.8
Radiotherapy and chemotherapy	555	4.9	5	59.1[b]	19.0–137.8
Female breast					
Chemotherapy only	318	4.7	1	34.9	0.5–194.0
Radiotherapy and chemotherapy	555	4.9	3[d]	55.6[b]	11.2–162.6
Melanoma of the skin					
Radiotherapy and chemotherapy	555	4.9	3[e]	26.9[b]	5.4–78.6
Oral cavity and pharynx[f]					
Surgery only	480	10.6	1	23.8	0.3–132.3
Radiotherapy only	102	7.9	1	141.4[b]	1.8–786.9
Radiotherapy and chemotherapy	555	4.9	1	42.2	0.6–234.8
AML[g]					
Radiotherapy and chemotherapy	555	4.9	3	99.6[b]	20.0–290.9

STS: soft tissue sarcoma; PYR: person-years at risk; O/E: observed-to-expected ratio; 95% CI: 95% confidence interval; AML: acute myeloid leukemia.

[a] Patients also may have undergone surgery.

[b] Statistically significant ($P < 0.05$).

[c] Six of the 7 children who received initial radiation developed a second sarcoma within the radiation field, all of which occurred 51–180 months after initial diagnosis.

[d] Two breast cancers developed within the radiation field 135 months and 160 months after the initial STS diagnosis.

[e] None of the melanomas could be categorized as occurring within or near the STS radiation field.

[f] One cancer of the buccal cavity developed near the STS radiation field.

[g] The total number of patients with AML included one patient who was diagnosed with AML after unknown treatment.

Risk by STS Histologic Type

Relative risks of developing second cancers were increased significantly among children who were diagnosed with rhabdomyosarcoma (O/E ratio = 7.7), fibromatous neoplasms (O/E ratio = 5.8), and other specified STS types (O/E ratio = 6.5) (Table 3). Initial treatment with combined chemotherapy and radiotherapy was associated with a significantly increased risk of developing second cancers, ranging from 9-fold for patients with rhabdomyosarcoma to > 70-fold for patients with fibromatous neoplasms. Initial treatment with either chemotherapy or radiotherapy alone was not associated with a significantly increased risk of second cancers for patients with rhabdomyosarcoma or "other specified STS" based on the small numbers of cancers observed. However, the risk of second cancers was elevated significantly for patients with fibromatous neoplasms who received radiation alone (observed = 2 malignancies), but not chemotherapy alone (observed = 0 malignancies).

DISCUSSION

The current results from the SEER population-based cancer registries across the United States show that children treated for STS have a significantly increased risk of second cancers. It was estimated that the risks were increased six-fold to eight-fold among patients who received therapy for rhabdomyosarcoma, fibromatous neoplasms, or other specified types of STS. Significantly elevated risks were seen for AML, cutaneous melanoma, and cancers of the oral cavity, breast, bone, and soft tissue, with generally higher risks seen among patients who received combined radiation and chemotherapy during their initial course of treatment for STS.

Clinical surveys of children who were treated for rhabdomyosarcoma have reported an increased incidence of new malignancies, especially for those receiving combined modality therapy.[2,3] The observed excess of AML in these trials was attributed to therapy with alkylating agents and topoisomerase II inhibitors

TABLE 3
The Risk of Second Cancer among 1-Year Survivors of Childhood Soft Tissue Sarcoma According to Histologic Type

Second cancer	No. of patients with STS	Median PYR	Total survivors ≥ 1 yr		
			Observed	O/E	95% CI
All histologic types[a]	1499	7.1	28	6.3[b]	4.2–9.1
Rhabdomyosarcoma and embryonal sarcoma	652	6.0	11	7.7[b]	3.9–13.8
Radiotherapy only	11	19.4	0	—	—
Chemotherapy only	193	5.0	2	5.8	0.7–20.9
Radiotherapy and chemotherapy	404	5.4	7	9.0[b]	3.6–18.5
Fibrosarcoma, neurofibrosarcoma, and other fibromatous neoplasms	402	9.6	9	5.8[b]	2.6–11.0
Radiotherapy only	34	8.0	2	19.2[b]	2.2–69.4
Chemotherapy only	34	3.6	0	—	—
Radiotherapy and chemotherapy	28	3.3	5	72.7[b]	23.4–169.6
Other specified STS	310	6.5	7	6.5[b]	2.6–13.4
Radiotherapy only	40	5.7	0	—	—
Chemotherapy only	61	6.6	0	—	—
Radiotherapy and chemotherapy	84	4.1	6	23.6[b]	8.6–51.3
Unspecified STS	135	4.5	1	2.4	0.0–13.5

STS: soft tissue sarcoma; PYR: person-years at risk; O/E: observed-to-expected ratio; 95% CI: 95% confidence interval.

[a] Histologic STS types were grouped according to the International Classification of Childhood Cancers (see Ries et al., National Cancer Institute SEER Program, 1999[12]).

[b] Statistically significant ($P < 0.05$).

(doxorubicin, etoposide). In our series, three children who were treated in more recent calendar years developed AML soon after they received combined modality therapy. The increased risk of second sarcomas of the bone and soft tissue after pediatric STS has been reported in both clinical and registry-based surveys[2,4,6] and is consistent with studies of childhood cancers linking high-dose radiation and alkylating agent therapy with excess sarcomas.[14,15]

Our study also revealed significantly increased risks of breast cancer and malignant melanoma after combined modality therapy for pediatric STS. The appearance of excess breast cancers ≥ 10 years after STS is consistent with previous studies that related chest irradiation at a young age with an increased risk of breast cancer.[16] Chemotherapy appeared to be the strongest contributor to the melanoma excess, because none of the patients with melanoma were known to have developed the cancer within the radiation field. Previous studies have found that chemotherapy is associated with increased total body counts of atypical and acral nevi, which predispose to melanoma, particularly in the setting of immunologic defects.[17] It is noteworthy that an indistinct "melanoma/sarcoma" syndrome has been described that may represent a genetic constellation of multiple cancers.[18,19] Diagnostic uncertainties in distinguishing between certain forms of melanoma and STS also are possible.[20]

Our finding among childhood STS survivors of a late-appearing excess of cancers of the oral cavity was unexpected, because, to our knowledge, no previous study of STS has reported this association. However, an increased risk of oral cancers has been reported after other childhood tumors, notably Hodgkin lymphoma[21] and acute lymphocytic leukemia.[22] The 3 subsequent cancers of the oral cavity (tongue, tonsil, and mouth) in our study appeared 14–26 years after the patients received initial therapy, which underscores the need for extended follow-up to evaluate the long-term risks of second malignancies.

Genetic predisposition to STS is illustrated by the elevated risk documented in syndromes associated with germline mutations of tumor suppressor genes, notably, NF1, LFS, and retinoblastoma.[9] In a previous study of children with rhabdomyosarcoma, Heyn et al. determined that the majority of patients with second cancers from whom family histories were obtained had either NF1 or an array of tumors suggestive of LFS.[2] Although family history was unavailable in the SEER database, the cancer patterns in two children with double primary cancers that involved STS were consistent with NF1, whereas the combination of three primary tumors in one patient was strongly suggestive of LFS. Because the tumor spectrum of LFS includes soft tissue and osteogenic sarcomas, breast cancer, acute leukemia, and possibly melanoma,[9,23] genetic susceptibility may have contributed to the ex-

cess risk for the various cancers observed in our study. It also is noteworthy that patients with LFS have been reported to be especially prone to subsequent primary tumors, notably sarcomas, in the radiation field.[24]

An important advantage of the SEER database is the ability to study a large number of patients with a rare cancer in a population-based setting. However, the limitations of our study include incomplete information concerning treatment and other risk factors and the lack of ascertainment of second cancers among patients who migrated outside the SEER geographic catchment areas.

We conclude that both treatment effects and genetic factors contributed to the increased risk of second cancers in this series of children with STS. The estimates of cancer risk probably are conservative due to migration of cancer patients outside the SEER catchment areas and the under-ascertainment of new cancers among long-term survivors. Although cohorts with larger numbers and more precise treatment data will be needed to confirm our findings, we provide new information that combined modality therapy increases the risk of subsequent primary cancers in patients with all forms of STS. Further studies of childhood STS survivors are needed to evaluate the independent and combined effects of therapy and genetic susceptibility in the development of various types of second cancers.

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